



PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: application of: Keith R. McCrae

Application No.: 09/437,912

Group Art Unit: 1653

Filed: November 9, 1999

For: INHIBITION OF ANGIOGENESIS BY HIGH
MOLECULAR WEIGHT KININOGEN PEPTIDE
ANALOGS THEREOF

Examiner: H. Robinson

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**DECLARATION OF KEITH R. McCRAE, M.D. UNDER 37 C.F.R.
§1.132**

1. I, Keith R. McCrae, hereby declare and state as follows:
2. I am the inventor of the above-identified patent application. I have read the office action dated September 4, 2003 (Paper No. 24).
3. The application discloses an invention directed to a high molecular weight kininogen peptides for treating angiogenesis. The present invention is based upon the discovery that two-chain high molecular weight kininogen (HK_a) and selected peptides of HK_a inhibit endothelial cell proliferation and/or induce endothelial cell apoptosis. These activities confer upon the HK_a peptides of the invention the ability to inhibit cytokine-driven angiogenesis.

CERTIFICATE OF MAILING

UNDER 37 C.F.R. 1.8(a)

I hereby certify that this paper, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date indicated below, with sufficient postage, as first class mail, in an envelope addressed to: MS' AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

BY Ng Davis M. Collins

DATE: 1/6/04

4. One group of peptides, as claimed in claims 1 and 30, has the formula X_1 -His-Lys-X-Lys- X_2 wherein:

X is any amino acid,

X_1 is the segment, His-Gly-His-Glu-Gln-Gln-His-Gly-Leu-Gly-His-Gly (SEQ ID NO:1), or an N-terminal truncation fragment thereof containing at least one amino acid, and

X_2 is

(i) zero amino acids, or

(ii) the segment Leu-Asp-Asp-Asp-Leu-Glu-His-Gln-Gly-Gly-His-Val (SEQ ID NO:2), or a C-terminal truncation fragment thereof containing at least one amino acid.

5. One of ordinary skill in the art at the time my patent application was filed would have known that “N-terminal” refers to the end of a peptide that carries the amino acid that has a free alpha amino group. In SEQ ID NO:1, this is the amino acid His. One of ordinary skill in the art would have known that an “N-terminal truncation fragment” is a fragment generated by removing one or more contiguous amino acids from the N-terminus of a peptide, that is, from the *end* of the peptide that carries the free alpha amino group. Similarly, one of ordinary skill in the art at the time my patent application was filed would have known that “C-terminal” refers to the end of a peptide that carries the free alpha carboxy group. In SEQ ID NO:2, this is the amino acid Val. One of ordinary skill in the art would have known that a “C-terminal truncation fragment” is a fragment generated by removing one or more contiguous amino acids from the C-terminus of a peptide, that is, from the *end* of the peptide that carries the free alpha carboxy group.

6. The possible N-terminal truncation fragments of SEQ ID NO:1 are set forth in Table 1. The possible C-terminal truncation fragments of SEQ ID NO:2 are set forth in Table 2.

Table 1 - POSSIBLE N-TERMINAL TRUNCATION FRAGMENTS OF SEQ ID NO:1

SEQ ID NO:1 → His-Gly-His-Glu-Gln-Gln-His-Gly-Leu-Gly-His-Gly
Gly-His-Glu-Gln-Gln-His-Gly-Leu-Gly-His-Gly
His-Glu-Gln-Gln-His-Gly-Leu-Gly-His-Gly
Glu-Gln-Gln-His-Gly-Leu-Gly-His-Gly
Gln-Gln-His-Gly-Leu-Gly-His-Gly
Gln-His-Gly-Leu-Gly-His-Gly
His-Gly-Leu-Gly-His-Gly
Gly-Leu-Gly-His-Gly
Leu-Gly-His-Gly
Gly-His-Gly
Gly

Table 2 – POSSIBLE C-TERMINAL TRUNCATION FRAGMENTS OF SEQ ID NO:2

Leu-Asp-Asp-Asp-Leu-Glu-His-Gln-Gly-Gly-His-Val ← SEQ ID NO:2
Leu-Asp-Asp-Asp-Leu-Glu-His-Gln-Gly-Gly-His
Leu-Asp-Asp-Asp-Leu-Glu-His-Gln-Gly-Gly
Leu-Asp-Asp-Asp-Leu-Glu-His-Gln-Gly
Leu-Asp-Asp-Asp-Leu-Glu-His-Gln
Leu-Asp-Asp-Asp-Leu-Glu-His
Leu-Asp-Asp-Asp-Leu-Glu
Leu-Asp-Asp-Asp-Leu
Leu-Asp-Asp-Asp
Leu-Asp-Asp
Leu-Asp
Leu

7. Submitted herewith are two publications that demonstrate the meaning of the expressions “N-terminal truncation fragment” and “C-terminal truncation fragment” as understood in the art: Fisher *et al.*, *J. Biol. Chem.*, 270(39):23143-23149 (1995), and Maselli *et al.*, *J. Cell Sci.*, 115(9):1939-1949 (2002). Fisher *et al.*, submitted herewith as attachment 1, discloses a protein kinase “VanS”. The authors investigated the biological activity of the VanS cytoplasmic domain, comprising VanS amino acids Met⁹⁵ to Ser³⁸⁴. A peptide corresponding to the cytoplasmic domain was prepared. A library of *C-terminal truncation fragments* of the Met⁹⁵-Ser³⁸⁴ cytoplasmic peptide was then prepared (p. 23147, col. 1, “*Preparation of C-terminal Truncation Library Using Transposon Mutagenesis*”). C-terminal truncation fragments inhibiting the activity of another protein, PhoB, were selected from the library of fragments. The inhibitory C-terminal truncation fragments are shown schematically in Fig. 4 (page 23148). It is clear from Fig. 4 that each C-terminal truncation fragment was achieved by removal a block of contiguous amino acids from the parent peptide, starting from the C-terminus (amino acid Ser³⁸⁴).

8. Maselli *et al.*, *J. Cell Sci.*, 115(9):1939-1949 (2002), submitted herewith as attachment 2, describes a 34kDa actin-binding protein containing 295 amino acids, and a fragment containing amino acids 124-295 thereof. The fragment, designated as “CT-myc” by the authors, lacks the first 123 amino acids of the parent protein. This fragment can only be achieved by removal of the 123 contiguous amino acids starting from the N-terminal end of the 34kDa peptide. The authors refer to CT-myc as an *N-terminal truncation fragment*: “The N-terminal truncation fragment CT-myc...” (Maselli *et al.*, page 1941, col. 1 under “*Results*”).

9. It is postulated by the examiner that N-terminal truncation fragments and C-terminal truncation fragments can be prepared by removal of one or more *internal* amino acids from a peptide. The examiner’s interpretation is contrary to the understanding of these terms in the art, as illustrated above. Indeed, the molecule remaining after the removal of one or more *internal* amino acids from a parent peptide could not even be considered as a “fragment”. The correct designation for such a molecule is “deletion mutant”. A “fragment” of a peptide is understood in the art as meaning a molecule generated by removal of contiguous amino acids from either end of a parent peptide, which molecule shares 100% sequence identity with a segment of the parent peptide. The molecule that results from the deletion of internal amino acids from a peptide does not result in a molecule which has 100% sequence identity with a segment of the parent peptide. Thus, one of ordinary skill in the art would understand that the only possible N-terminal truncation fragments of SEQ ID NO:1 are the fragments listed in Table 1. Likewise, one of

ordinary skill in the art would understand that the only possible C-terminal truncation fragments of SEQ ID NO:2 are the fragments listed in Table 2.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued thereupon.

Date: 12/26/03

Keith R. McCrae MD
Keith R. McCrae, Ph.D.